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COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

December 21, 1999

Charles M. Auer
Director, Chemical Control Division
Office of Pollution Prevention and Toxics
US Environmental Protection Agency
401 M Street, S.W., MC 7405
Washington, DC 20460

RE: Test Plan for High Butadiene C4 Category

Dear Mr. Auer:

Enclosed is the test plan for the Olefins Panel's High Butadiene C4 Category under the HPV Chemical Challenge Program. The members of the Panel are listed in the test plan. We are also submitting robust summaries for existing data for the SIDS endpoints on substances included in the category. The test plan and robust summaries will also be submitted to you electronically.

If you have any questions, please call Dr. Elizabeth Moran, manager of the Olefins Panel, at 301/774-9231.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For The

CRUDE BUTADIENE C4 Category

Prepared by:

CMA Olefins Panel, HPV Implementation Task Group

May 1, 2000

PLAIN ENGLISH SUMMARY

This test plan addresses crude butadiene streams, which typically contain 10 to 92 percent 1,3-butadiene. Three substances will be evaluated: pure butadiene (already tested), a mid-range stream containing approximately 45-67 percent butadiene (also already tested), and a low concentration stream with approximately 10 percent butadiene (testing will be conducted). Based on existing data, the test sponsors believe the biological activity of each stream will be determined by the 1,3-butadiene content in the stream. These streams also contain other C4 substances. Additional data will be collected on these other substances, either under other test plans under the HPV Challenge Program, or through the OECD SIDS or ICCA program. The additional data will assist the test sponsors in determining whether 1,3-butadiene is the most biologically active component of the crude butadiene streams.

EXECUTIVE SUMMARY

The Chemical Manufacturers Association (CMA) Olefins Panel and its member companies hereby submit for review and public comment the test plan for the Crude Butadiene C4 category under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program (Program). It is the intent of the CMA Olefins Panel and its member companies to use new information in conjunction with a variety of existing data and scientific judgment/analyses to adequately characterize the SIDS (Screening Information Data Set) human health, environmental fate and effects, and physicochemical endpoints for this category.

This test plan addresses crude butadiene streams. Streams are mixtures of chemicals. In the case of crude butadiene streams, they are mixtures of butadiene and other chemicals, primarily chemicals containing 4 carbons. The major difference between the different crude butadiene streams is the amount of the various chemicals in the streams. Because butadiene is believed to be the most toxic chemical in the mixture, the strategy is to evaluate streams containing different concentrations of butadiene, covering the range of butadiene concentration found in these streams.

Crude butadiene streams typically contain 10 to 92 percent 1,3-butadiene, with the balance consisting predominantly of other C4 substances including 1-butene, 2-butene, isobutylene, butane and isobutane. The plan advocates addressing the category by evaluating three substances: pure butadiene (data already available), a mid-range stream containing approximately 45-67 percent butadiene (data already available), and a low concentration stream with approximately 10 percent butadiene (testing will be conducted). 1,3-Butadiene has been extensively studied and is in the SIDS process. The SIDS review is expected to be completed by the end of 2000. The test plan is based on the expectation that the presence of butadiene in the crude butadiene C4 streams will be responsible for the biological activity of the streams. This assumption is based in part on 1,3-butadiene data, and also on what is known about the other C4 compounds. Additional data will be collected on other C4 compounds as part of other test plans under the HPV Challenge Program, the ICCA program, or from chemicals already sponsored in the OECD SIDS program. The additional data will assist the Panel in determining whether butadiene is the most biologically active component of the Crude Butadiene C4 streams.

One crude butadiene stream is the full range butadiene concentrate. This stream is a mixture of butadiene, other chemicals containing 4 carbons, and other chemicals with fewer than or more than 4 carbons. Benzene is a significant component of the full range butadiene concentrate. The complete characterization of the full range butadiene concentrate stream will be accomplished by use of data from this test plan along with data from other Olefins

Panel categories (including a category with streams containing benzene) and from the data on benzene itself, which is in the SIDS process.

Predictive computer models will be used to develop much of the aquatic toxicity, environmental fate, and physicochemical data for substances in the Crude Butadiene C4 category. Aquatic toxicity testing procedures were not designed for gaseous substances like those in this category and testing will not be conducted. However, relevant information will be provided in a technical discussion that addresses the physical nature of these substances and includes a discussion of calculated aquatic toxicity data. The calculated data will be developed from a computer model used by the EPA. Relevant environmental fate information will be summarized either through the use of computer models when meaningful data can be developed or in technical discussions when computer modeling is not applicable. Physicochemical properties will be represented as a range of values according to component composition. These data will be calculated using a computer model cited in an EPA guidance document prepared for the HPV Challenge Program.

LIST OF MEMBER COMPANIES

THE OLEFINS PANEL

The Chemical Manufacturers Association (CMA) Olefins Panel includes the following member companies:

BP Amoco, p.l.c.
Chevron Chemical Company LLC
CONDEA Vista Company
The Dow Chemical Company
E. I. du Pont de Nemours and Company
Eastman Chemical Company
Equistar Chemicals, LP
ExxonMobil Chemical Company
Fina Oil and Chemical Company*
Formosa Plastics Corporation, U.S.A.
The B.F.Goodrich Company*
The Goodyear Tire & Rubber Company
Huntsman Corporation
Koch Industries*
NOVA Chemicals Inc.
Phillips Chemical Company
Shell Chemical Company
Sunoco, Inc.*
Texas Petrochemicals Corporation
Union Carbide Corporation
Westlake Chemical Corporation
Williams Olefins, LLC

* These companies are part of the Olefins Panel but do not produce CAS numbers in the Crude Butadiene C4 Category.

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TEST PLAN FOR THE CRUDE BUTADIENE C4 CATEGORY

I. INTRODUCTION

The Chemical Manufacturers Association (CMA) Olefins Panel (Panel) and its member companies have committed voluntarily to develop screening level human health effects, environmental effects and fate, and physicochemical test data for the Crude Butadiene C4 category under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge Program (Program).

This plan identifies CAS numbers used to describe process streams in the category, identifies existing data of adequate quality for substances included in the category, and outlines testing planned to develop screening level data for this category under the Program. This document also provides the testing rationale for the Crude Butadiene C4 category. The objective of this effort is to identify and develop sufficient test data and/or other information to adequately characterize the human health and environmental fate for the category in compliance with the EPA HPV Program. Physicochemical data that are requested in this program will be calculated as described in EPA guidance documents.

II. DESCRIPTION OF THE CRUDE BUTADIENE C4 CATEGORY

A. The Category

The Crude Butadiene C4 Category was developed by grouping process streams that the Panel believes are similar from both a process and toxicology perspective. Twelve CAS numbers (Table 1) are used to describe these process streams. A process stream is a mixture of chemicals that arises from a chemical reaction or separation activity. Those mixtures containing 10 to 92% butadiene are referred to as "crude butadiene." With the exception of CAS 106-99-0 (which is pure 1,3-butadiene), the CAS numbers or streams in this category consist of complex mixtures of hydrocarbons. Most of the commercial products in this category have a carbon number distribution predominantly between C3 and C5. All these streams contain significant levels of 1,3-butadiene and olefins, which is why this group is considered a category for purposes of the HPV Program, and designated Crude Butadiene C4. The definitions found in the TSCA Chemical Substance Inventory for the CAS numbers included in this group are vague with respect to composition. Therefore, it is not uncommon to find that the same CAS number is correctly used to describe different streams (compositions) or that two or more different CAS numbers are used to describe the same stream (composition or process).

The crude butadiene streams arise from production processes associated with ethylene manufacturing. A description of the ethylene and associated processes is included in Appendix I. Briefly, the three process streams (sometimes referred to as products) are:

(1) Butadiene concentrate arises from the distillation of cracked gas. This typically contains 40% to about 60% 1,3-butadiene (table 2), but could contain between 10% and 80% butadiene. Other chemicals in this mixed stream are predominately chemicals containing 4 carbons.

(2) High butadiene heavy ends from the butadiene plant that arise from extractive distillation. The 1,3-butadiene content of this mixed stream ranges from 13% to 92% (table 2). Other chemicals in this mixed stream are predominately chemicals containing 4 carbons.

(3) Full-range butadiene concentrate which is the mixed stream remaining after the removal of ethylene. The 1,3-butadiene content of full range butadiene concentrate has been reported to range from 12% to 42% (table 2). Other chemicals in this mixed stream are those containing three to twelve carbons.

Note that any of the CAS numbers in this category (except the CAS number for 1,3-butadiene itself) can be used correctly to describe any of the mixed streams discussed above.

III. TEST PLAN RATIONALE

A. Overview

1. Butadiene Concentrate and Heavy Ends

Much of existing data for the Crude Butadiene C4 category are for 1,3-butadiene (Table 3), the hydrocarbon substance which is likely the most biologically active of the substances in the category and thus the major contributor to toxicological activity. 1,3-Butadiene itself is in the SIDS process and the review is expected to be completed by the end of 2000. Because of the SIDS review, butadiene has, or should have in the future, existing data of adequate quality for each of the end points. A possible exception is the acute inhalation toxicity study. The acute toxicity study included in the robust summaries, which are submitted as a separate document, contained insufficient experimental detail to assess quality. However, 1,3-butadiene has been extensively studied and acute toxicity is clearly not an issue. Our understanding of the toxicity of 1,3-butadiene would not be improved by repeating the acute toxicity study. Therefore, it was decided that the existing study was sufficient to address the acute toxicity endpoint for 1,3-butadiene. There are also data available for two crude butadiene streams. The compositions of the two previously tested crude butadiene streams were: (1) 45% 1,3-butadiene, 20% butanes, and 30% butenes and (2) 67% 1,3-butadiene, 30% butenes, and 2% 1,2-butadiene. 1,3-Butadiene is present in all the CAS numbers in this category. The presence of this chemical at concentrations >10% by weight creates a presumption under the Program that the substance would result in positive genotoxicity as the most sensitive endpoint. Supporting this presumption, the crude butadiene feedstock containing 45% butadiene has

been shown to be genotoxic.

To verify the relevance of the extrapolation of 1,3-butadiene data to substances with lower 1,3-butadiene concentrations, a full SIDS human health test battery will be conducted for a process stream containing approximately 10% 1,3-butadiene. This process stream will also include other chemicals that are included in the other streams that make up this category. The exact composition of the stream to be tested will be determined analytically at the time of testing.

The data for 1,3-butadiene together with the data from the low (approximately 10%) 1,3-butadiene-containing process stream and the data from the mid-level (45-67%)1,3-butadiene streams will be sufficient to adequately characterize the range of substances included in the category and the associated potential human health effects under the HPV Program. Crude butadiene (full range) also contains benzene. It is anticipated that similar cytogenic effects (micronuclei induction, etc.) will result from benzene, based on knowledge of the existing SIDS data set for benzene. However, it is proposed to complete a full HPV SIDS test battery for a benzene-containing stream in the High Benzene Naphtha category (volunteered for testing in 2001). The information obtained from testing a High Benzene Naphtha stream will be used in conjunction with the information obtained from testing the Crude Butadiene C4 stream described above to fully characterize the full range product.

Environmental fate and effects test data for the required endpoints do not exist for substances in this category (Table 3). This is not unexpected because these CAS numbers represent mixtures of gaseous substances and therefore, are not appropriate to be evaluated using existing standard testing guidelines. In addition, because these substances are gases, it is highly unlikely that they will pose a hazard to aquatic or terrestrial environments. As a result, aquatic toxicity and biodegradation testing will not be conducted based on the physical state of these substances and their physicochemical parameters (i.e., low boiling point, high volatility, and high Henry's Law constants). However, the environmental endpoints for photodegradation, hydrolysis, transport, and fugacity will be either calculated or discussed.

Structure-activity relationships (SARs) can be used to calculate transport (Koc) and fugacity, the latter of which is only calculated. Components of process streams in the category will partition primarily to the air, and because they have relatively low Kow values, their fate in air is the focus of environmental interest. In addition, these low Kow values suggest that they will not partition to suspended organic matter in air and therefore they will not precipitate to aquatic and terrestrial compartments.

In all cases, based on physicochemical characteristics, these substances will partition to the air at a rapid rate if released to the environment. As a result, the aquatic and terrestrial environments will not be the compartments of concern when evaluating the potential environmental impact of these substances. However, there are SARs that can be used to evaluate the potential toxicity of chemicals. A SAR will be used to calculate the toxicity of selected chemical components of the Crude Butadiene C4 category.

2. Full-Range Butadiene Concentrate

To completely characterize the toxicity of the full-range butadiene concentrate streams, data from the Crude Butadiene C4 category will be combined with data obtained during the assessment of other categories under the Olefins Panel's HPV program. Specifically, the data for the Crude Butadiene C4 category, the C-5 category, the High Benzene Naphtha category which contains benzene, and the C-3 streams category, which contains other 3 carbon compounds will, taken together, completely characterize the toxicity of this stream. Additionally, as noted, the available SIDS data sets on 1,3-butadiene and benzene will be used to assess two major determinants of toxicity of these streams.

B. Human Health Effects

1,3-butadiene (CAS #106-99-0) is likely the most biologically active component of the process streams in the Crude Butadiene C4 category. There are existing data for 1,3-butadiene, which is a SIDS listed material. The toxicity of other major components (primarily butanes and butenes), is known or will be known from current or planned testing to be sponsored by the Chemical Manufacturers Association and American Petroleum Institute. For more details on other test categories, see Section V - Other Relevant Data.

The toxicity of butadiene can be used to characterize the Crude Butadiene C4 streams represented by the CAS numbers in the category, because butadiene is typically present at greater than 10 percent. It is anticipated that positive genotoxicity will be the health effect endpoint most likely to show a positive response at the lowest test concentration for this category.

To confirm the relevance of the extrapolation of data from category members with high 1,3-butadiene content to process streams with a similar carbon number range but with lower butadiene content, a full test battery is recommended for a stream containing approximately 10% butadiene. The exact composition of the low 1,3-butadiene containing stream will be determined analytically at the time of testing. Health effects testing will be conducted by the inhalation route and will consist of the acute toxicity, Ames, mouse micronucleus, and combined repeat dose/reproductive effects/neurotoxicity screen. Of the SIDS endpoints, only the mouse micronucleus test is known to show a dose-related adverse response with butadiene exposure and with the exception of acute central nervous system effects, no other significant adverse effects have been identified in the SIDS testing conducted on other C4 substances. Additional data on other C4 components will become available through the SIDS, ICCA, and HPV programs to complete the data base for these compounds (see Section VI).

It is anticipated that the biological spectrum of activity for 1,3-butadiene, with regard to positive genotoxicity, may be reflected in the other process streams in the category. Since metabolism of butadiene is required for toxicity, and other C4 alkenes are metabolized through a common metabolic pathway, it is anticipated that mixed components will compete

for the same active enzyme sites. Different individual toxicities, which are dependent on the formation of biologically active metabolites, may be reduced, as less metabolite(s) will be produced through competition for these sites. Hence the positive genotoxicity of butadiene may in fact be reduced or eliminated by the greater presence of the other components. This is supported by existing test data for a feedstock stream containing 45% butadiene which appears to be less genotoxic than 1,3-butadiene per se. This will be further assessed by testing a stream containing a low concentration (approximately 10%) of 1,3-butadiene.

This recommended testing, in conjunction with existing data and data under development for selected components of the process streams covered by this category, will provide adequate data to characterize the Crude Butadiene C4 category for human health effects endpoints under the Program.

C. Ecotoxicity

There are three aquatic toxicity endpoints in the HPV Program:

- Acute Toxicity to Fish
- Acute Toxicity to Aquatic Invertebrates
- Toxicity to Algae (Growth Inhibition)

EPA identifies the following test methods to determine these endpoints: OECD Guideline 203, *Fish Acute Toxicity Test*; Guideline 202, *Daphnia sp., Acute Immobilization Test*; and Guideline 201, *Alga Growth Inhibition Test* [2].

The OECD aquatic toxicity test methods were not designed to assess the acute toxicity of gaseous substances like those in the Crude Butadiene C4 category. Therefore, the Panel will develop a Robust Summary Statement that addresses the physical nature of these substances and the fact that their primary route of loss will be to the air. This discussion will include calculated toxicity data for selected chemical components. The calculated data will be developed using ECOSAR, a SAR program found in EPIWIN [1].

D. Environmental Fate

Predictive models will be used to develop meaningful data for chemicals that are gaseous at relevant environmental temperatures and pressures. The environmental fate data include:

- Photodegradation
- Stability in Water (Hydrolysis)
- Transport and Distribution (Fugacity)
- Biodegradation

1. Photodegradation

Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance. If the absorbed energy is high enough then the resultant excited state of the chemical may undergo a transformation. Simple chemical structures can be examined to determine whether a chemical has the potential for direct photolysis in water. First order reaction rates can be calculated for some chemicals that have a potential for direct photolysis using the procedures of Zepp and Cline [2].

Photodegradation can be measured [3] (EPA identifies OECD test guideline 113 as a test method) or estimated using models accepted by the EPA [4]. An estimation method accepted by the EPA includes the calculation of atmospheric oxidation potential (AOP). Atmospheric oxidation as a result of hydroxyl radical attack is not direct photochemical degradation, but rather indirect degradation. AOPs can be calculated using a computer model. Chemicals that are gases will be available for atmospheric oxidation reactions with photochemically generated hydroxyl radicals. This will be the most significant route of degradation in the environment for category members.

The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) [1] is used by OPPTS. This program calculates a chemical half-life based on an overall OH reaction rate constant, a 12-hr day, and a given OH concentration. This calculation will be performed for representative chemical components identified in the Crude Butadiene C4 category.

2. Stability in Water (Hydrolysis Testing and Modeling)

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters [5]. Stability in water can be measured [3] (EPA identifies OECD test guideline 111 as a test method) or estimated using models accepted by the EPA [4]. An estimation method accepted by the EPA includes a model that can calculate hydrolysis rate constants for esters, carbamates, epoxides, halomethanes, and selected alkylhalides. The computer program HYDROWIN (aqueous hydrolysis rate program for Microsoft windows) [1] is used by OPPTS.

It will not be necessary to run the model for the components of the streams in this category because the model cannot estimate their hydrolysis rate. Instead, a technical discussion as to why these chemicals would not be subject to hydrolysis will be prepared.

3. Chemical Transport and Distribution In The Environment (Fugacity Modeling)

Fugacity based multimedia modeling can provide basic information on the relative distribution of chemicals between selected environmental compartments (i.e., air, soil, sediment, suspended sediment, water, biota). The US EPA has acknowledged that computer modeling techniques are an appropriate approach to estimating chemical partitioning (fugacity is a

calculated endpoint and is not measured). A widely used fugacity model is the EQC (Equilibrium Criterion) model [6]. EPA cites the use of this model in its document titled *Determining the Adequacy of Existing Data* [3], which was prepared as guidance for the HPV Program.

In its document, EPA states that it accepts Level I fugacity data as an estimate of chemical distribution values. The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as percent partitioned to 6 compartments within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition.

The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment. This model will be used to calculate distribution values for representative chemical components identified in streams in this category. A computer model, EPIWIN - version 3.02 [1], will be used to calculate the properties needed to run the Level I EQC model.

4. Biodegradation Testing

Biodegradation is the utilization of a chemical by microorganisms as a source of energy and carbon. The parent chemical is broken down to simpler, smaller chemicals, which are ultimately converted to an inorganic form such as carbon dioxide, nitrate, sulfate, and water. Assessing the biodegradability of organic chemicals using a standard testing guideline can provide useful information for evaluating chemical hazard.

Substances in this category are gaseous at room temperature. Standard OECD biodegradation test methods were not designed to assess the relative biodegradability of gaseous materials. To provide relevant information for this endpoint, a discussion will be developed on the physical nature of these substances and the fact that their primary route of loss will be to the air compartment where they will degrade through hydroxyl radical attack, which is briefly described under *photodegradation* above.

E. Physicochemical Properties

The physicochemical properties include:

- Melting Point
- Boiling Point
- Vapor Pressure
- Octanol/Water Partition Coefficient
- Water Solubility

Because the HPV substances covered under the Olefins Crude Butadiene C4 category testing plan are variable mixtures, it is not possible to develop or calculate a single numerical value for some of the physicochemical properties. For example, a product that is a mixture of chemicals does not have a melting point, but rather a melting range. Values for physicochemical properties will be represented as a range of values according to the product's component composition and based on the results of computer modeling.

Data for the physicochemical endpoints will be developed using sources recommended by EPA. There are estimation models (Structure-Activity Relationships, SAR) for each of these endpoints in the EPIWIN [1] (Estimation Program Interface for Windows) computer program and EPA has indicated that it will accept estimated data using this program [4].

Boiling point, melting point, and vapor pressure ranges will be determined using the MPBPVP subroutine in EPIWIN. K_{ow} and water solubility will be calculated using KOWIN and WSKOW subroutines, respectively. There is more information on calculating data for the HPV chemical program in the EPA document titled, *The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program.*

IV. TEST PLAN SUMMARY

The following testing, modeling, and technical discussions will be developed for the Crude Butadiene C4 category (Table 3):

- Conduct one test battery for all SIDS human health endpoints on a product (stream) containing approximately 10% 1,3-butadiene (exact composition to be determined at the time of testing).
- Compare evaluated endpoints to those for 1,3-butadiene and the other identified data and prepare a technical discussion in terms of their representation of potential human health effects for this category.
- Prepare a technical discussion of the potential aquatic toxicity of selected chemical components comprising streams in this category using modeled data.
- Prepare a technical discussion on the potential of chemical components comprising streams in this category to photodegrade.
- Prepare a technical discussion on the potential of chemical components comprising streams in this category to hydrolyze.
- Prepare a technical discussion on the potential biodegradation of chemical components of streams in this category.
- Calculate fugacity data for selected chemical components of streams in this category.
- Calculate physicochemical data as described in the EPA document titled, *The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program.*

Summaries of results will be developed once the data and analyses are available. This test plan is expected to provide adequate data to characterize the human health effects and environmental fate and effects endpoints for the category under the Program.

V. OTHER RELEVANT DATA

The Crude Butadiene C4 test category addresses crude butadiene streams, which typically contain 10 to 92 percent 1,3-butadiene, with the balance consisting predominantly of other C4 substances including 1-butene, 2-butene, isobutylene, butane and isobutane. The plan proposes addressing the category using data for three substances: pure butadiene, a mid-range stream containing approximately 45-60 percent butadiene, and a low concentration stream with approximately 10 percent butadiene. The test plan is based on the expectation that the biological activity of 1,3-butadiene will be responsible for the effects seen in the testing of the crude butadiene streams. This assumption is based in part on 1,3-butadiene data, and also what is known about the other C4 compounds. Additional data will be collected on other components of these streams as part of other test plans under the HPV Challenge Program, the ICCA program, or from chemicals already sponsored in the OECD SIDS program.

Propane and propylene account for most of the C3 materials found in the crude butadiene streams. The Petroleum HPV Test Group, managed by API, has taken responsibility for propane under the HPV program. The data set for propylene is expected to be covered under the ICCA program.

Major C4 components other than 1,3-butadiene, commonly present in crude butadiene streams included butane, isobutane, 1-butene, isobutylene and 2-butene. The Petroleum HPV Test Group has taken responsibility for butane and isobutane. The CMA Olefins Panel will complete the data set for 1-butene as part of a separate test category (Category 2 Low butadiene C4). Isobutylene and 2-butene are already in the OECD SIDS program. Therefore, data already exists or will be developed for each of the major C4 components in the Crude Butadiene C4 category.

The full-range butadiene concentrate stream included in this test category consists of the entire C3+ or C4+ compounds produced in the cracking furnace. This stream is only rarely isolated and is usually site-limited. Normally this stream is further processed by distillation into a C3 fraction (propylene stream), a C4 fraction (C4 butadiene concentrate) and a C5+ fraction (pyrolysis gasoline). A separate test plan, sponsored by the CMA Olefins Panel, will be submitted for the C3 fraction. The C4 fraction is the material of primary interest in this test category. Testing of the C5+ fraction will be done under separate test categories sponsored by the CMA Olefins panel. More specifically, a separate test plan will be submitted for the C3 propylene stream, for the predominantly C5 category, for a C6+ high benzene naphtha category and for a low benzene naphtha category. For a complete list of test categories sponsored by the CMA Olefins Panel see table 4. It is also worth noting that in addition to 1,3-butadiene, many of the other major components found in the full-range butadiene

concentrate stream are in the OECD SIDS program including benzene, toluene and dicyclopentadiene. While testing a C3+ or C4+ stream is not specifically proposed, sufficient data will become available to characterize this material as a result of the testing of the various cuts previously mentioned.

REFERENCES

1. EPIWIN. 1999. Estimation Program Interface for Windows, version 3.02. Syracuse Research Corporation, Syracuse, NY, USA.
2. Zepp, R. G., and D. M. Cline. 1977. Rates of Direct Photolysis in the Aqueous Environment. Environ. Sci. Technol. 11:359.366.
3. US EPA. 1999. Determining the Adequacy of Existing Data. OPPT, EPA.
4. US EPA. 1999. The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.
5. Neely, W. B. 1985. Hydrolysis. In: W. B. Neely and G. E. Blau, eds. Environmental Exposure from Chemicals. Vol I., pp. 157-173. CRC Press, Boca Raton, FL, USA.
6. Mackay, D., A. Di Guardo, S. Paterson, and C. E. Cowan. 1996. Evaluating the Environmental Fate of a Variety of Types of Chemicals Using the EQC Model. Environ. Toxicol. Chem. 15:1627-1637.

Table 1. CAS Numbers And Descriptions.

CAS Number	CAS Number Description
106-99-0	1,3-Butadiene
25167-67-3	Butenes
68477-41-8	Distillate (Petroleum), Extractive C3-5
68955-28-2	Gases, (Petroleum) Light Steam Cracked, Butadiene Conc.
68476-44-8	Hydrocarbons, >C3
68512-91-4	Hydrocarbons C3 – C4 rich petroleum distillates
68187-60-0	Hydrocarbons, C4, Ethane-Propane Cracked
68476-52-8	Hydrocarbons, C4, Ethylene Manufactured By-Product
68956-54-7	Hydrocarbons C4, unsaturated
69103-05-5	Hydrocarbons, C4-7, Butadiene Manufactured By-Product
64742-83-2	Naphtha, (Petroleum), Light Steam-Cracked
68513-68-8	Residues (Petroleum), Deethanizer Tower

Table 2. Typical Composition Ranges (Percent) For Crude Butadiene Streams

Component	Crude Butadiene or Butadiene Concentrate	Heavy Ends	Full-Range Butadiene Concentrate
Tert-butyl catechol	0 - 0.01		
Methanol	0.0 - 0.3		
Propylene	0.0 - 1.9		0 - 4.0
Other C3 &lighter	0.5 - 1.7		0 - 1.0
Methylacetylene & Propadiene	0.0 - 2.3		
Ethyl & Vinylacetylene	0.7 - 3.0		
Isobutane	0.4 - 22		0.0 - 1.1
n-Butane	1.5 - 30	0.0 - 6.0	1.0 - 4.5
Isobutylene	0.5 - 29		5.0 - 12
cis & trans-butene-2	3.5 - 54	5 - 50	1.5 - 6.4
Butene-1	2.5 - 25	0.0 - 4.0	5.0 - 11
1,3-Butadiene	**10 - 82**	**13 - 92**	**12 - 42**
1,2-Butadiene	0.0 - 1.4	0.0 - 2.0	0.0 - 1.0
C5 & Higher	0.0 - 8.0		
Vinylcyclohexene	0.0 - 1.0		
Isopentane		0.0 - 3.0	
C8		0.0 - 4.0	
1,4-pentadiene			0.2 - 1.2
Pentene-1			0.5 - 2.3
Isoprene			0.6 - 3.2
cis & trans-pentene-2			0.1 - 2.0
1,3-cyclopentadiene			1.0 - 9.5
cis & trans-1,3-pentadiene			1.0 - 7.2
cyclopentene			0.5 - 2.6
cyclopentane			2.0 - 4.0
C6-C8 non-aromatics			2.0 - 12
Benzene			11 - 42
Toluene			1.8 - 25
Xylenes			0.1 - 4.0
Ethylbenzene			0.1 - 1.3
Dicyclopentadiene			2.0 - 10
Indene			0.3 - 1.9
Naphthalene			0.2 - 1.6
Other C9 and higher			1.5 - 8.7

Note 1:The balance of these streams is expected to be other hydrocarbons that have boiling points in the range of the listed components.
Note 2: The listed highs and lows should not be considered absolute values for these limits. They are instead the highs and lows of the reported values, and are expected to be typical limit values.
Note 3: The definitions, found in the TSCA Chemical Substance Inventory, for the CAS numbers included in this group are vague with respect to composition. Therefore, it is not uncommon to find that the same CAS number is correctly used to describe different streams (compositions) or that two or more different CAS numbers are used to describe the same stream (composition).

Table 3. Assessment Plan For Crude Butadiene C4 Category Under The Program. Robust summaries for existing studies are submitted separately.

Product Description	Human Health Effects						Ecotoxicity			Environmental Fate				
	Acute Toxicity	**Genetic Point Mut.**	**Genetic Chrom.**	**Sub-chronic**	**Develop-mental**	**Reproduc-tion**	**Acute Fish**	**Acute Invert.**	**Algal Toxicity**	**Physical Chem.**	**Photo-deg.**	**Hydro-lysis**	**Fugacity**	**Biodeg.**
1,3-Butadiene	**v**	**v**	**v**	**v**	**v**	**v**[1]	NA	NA	NA	SAR	TD	TD	CM	TD
Mid-range 1,3-Butadiene- 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene	RA	**v**	RA	RA	RA	RA	NA	NA	NA	SAR	TD	TD	CM	TD
Mid-range 1,3-Butadiene 45% 1,3-butadiene, 20% butanes, 30% butenes	**v**	**v**	**v**	**v**	RA	RA	NA	NA	NA	SAR	TD	TD	CM	TD
Low 1,3-Butadiene[2]	T	T	T	T	T	T	NA	NA	NA	SAR	TD	TD	CM	TD

v	Adequate existing data available	TD	Technical discussion proposed	SAR	Structure Activity Relationship
1	These data are not yet available, but should be addressed as part of the SIDS program	CM	Computer Modeling proposed		
		RA	Read Across		
2	The target concentration of 1,3-butadiene is 10%. Actual composition will be determined analytically and provided when testing is complete.				
NA	Test not applicable due to physical nature of category member	T	Proposed Testing		

Appendix I

ETHYLENE PROCESS DESCRIPTION

A. The Ethylene Process

1. Steam Cracking

Steam cracking is the predominant process used to produce ethylene. Various hydrocarbon feedstocks are used in the production of ethylene by steam cracking, including ethane, propane, butane, and liquid petroleum fractions such as condensate, naphtha, and gas oils. The feedstocks are normally saturated hydrocarbons but may contain minor amounts of unsaturated hydrocarbons. These feedstocks are charged to the coils of a cracking furnace. Heat is transferred through the metal walls of the coils to the feedstock from hot flue gas, which is generated by combustion of fuels in the furnace firebox. The outlet of the cracking coil is usually maintained at relatively low pressure in order to obtain good yields to the desired products. Steam is also added to the coil and serves as a diluent to improve yields and to control coke formation. This step of the ethylene process is commonly referred to as "steam cracking" or simply "cracking" and the furnaces are frequently referred to as "crackers".

Subjecting the feedstocks to high temperatures in this manner results in the partial conversion of the feedstock to olefins. In the simplest example, feedstock ethane is partially converted to ethylene and hydrogen. Similarly, propane, butane, or the hydrocarbon compounds that are associated with the liquid feedstocks are also converted to ethylene. Other valuable hydrocarbon products are also formed, including other olefins, diolefins, aromatics, paraffins, and lesser amounts of acetylenes. These other hydrocarbon products include compounds with two or more carbon atoms per molecule, i.e., C2, C3, C4, etc. Propane and propylene are examples of C3 hydrocarbons and benzene, hexene, and cyclohexane are a few examples of the C6 hydrocarbons.

2. Refinery Gas Separation

Ethylene and propylene are also produced by separation of these olefins streams, such as from the light ends product of a catalytic cracking process. This separation is similar to that used in steam crackers, and in some cases both refinery gas streams and steam cracking furnace effluents are combined and processed in a single finishing section. These refinery gas streams differ from cracked gas in that the refinery streams have a much narrower carbon number distribution, predominantly C2 and/or C3. Thus the finishing of these refinery gas streams yields primary ethylene and ethane, and/or propylene and propane.

B. Products of the Ethylene Process

The intermediate stream that exits the cracking furnaces (i.e., the furnace effluent) is

forwarded to the finishing section of the ethylene plant. The furnace effluent is commonly referred to as “cracked gas” and consists of a mixture of hydrogen, methane, and various hydrocarbon compounds with two or more carbon atoms per molecule (C2+). The relative amount of each component in the cracked gas varies depending on what feedstocks are cracked and cracking process variables. Cracked gas may also contain relatively small concentrations of organic sulfur compounds that were present as impurities in the feedstock or were added to the feedstock to control coke formation. The cracked gas stream is cooled, compressed and then separated into the individual streams of the ethylene process. These streams can be sold commercially and/or put into further steps of the process to produce additional materials. In some ethylene processes, a liquid fuel oil product is produced when the cracked gas is initially cooled. The ethylene process is a closed process and the products are contained in pressure systems. (See figure 1 for a pictorial representation of the ethylene manufacturing process.)

The final products of the ethylene process include hydrogen, methane (frequently used as fuel), and the high purity products ethylene and propylene. Other products of the ethylene process are typically mixed streams that are isolated by distillation according to boiling point ranges. It is a subset of these mixed streams that make up the constituents of the Crude Butadiene C4 category.

C. The Crude Butadiene C4 Products

1. Crude Butadiene Or Butadiene Concentrate

Butadiene concentrate is the product in the C4 Crude Butadiene Category. The concentrate is separated by distillation from the condensed portion of the cracked gas. Typically, butadiene concentrate is a fairly narrow boiling range mixture and consists predominately of C4 hydrocarbons. The butadiene concentrate may also contain lesser amounts of C3 or lighter hydrocarbons and C5 and heavier hydrocarbons, because the separation technology is not perfect. The 1,3-butadiene content of this product is typically 40% to 60%, but has been reported to range from 10% to about 80% (table 2). Crude butadiene is sometimes produced in "on purpose" butadiene units using, for example, an oxydehydrogenation process.

2. High Butadiene-Content Heavy Ends From The Butadiene Plant

Several different technologies are used to separate 1,3-butadiene from C4 butadiene concentrate produced by the ethylene process. All of these processes use a solvent for the separation.

In one technology, the C4 butadiene concentrate is fed to an extractive distillation (ED) column and a C4 mixture referred to as “raffinate” (i.e., C4 olefins and paraffins) is separated from the top of the distillate column. The bottom from the ED column consists of the solvent, rich in 1,3-butadiene, and small amounts of other C4s. The rich solvent is fed to the solvent stripper where the 1,3-butadiene and other C4s are taken overhead. The stripped, lean solvent is transferred from the bottom of the stripper back to the ED tower. The overhead of the

stripper is condensed and fed to the rerun tower (or postfractionator) where high purity 1,3-butadiene is produced as the overhead. Bottoms of the rerun tower consist of the higher boiling components of the butadiene concentrate (e.g., 1,2-butadiene). The 1,3-butadiene content of the heavy ends from the butadiene plant covered by this test plan ranges from 13% to 92% (table 2).

3. Full-Range Butadiene Concentrate

Butadiene concentrate sometimes consists of the entire C3+ or C4+ portion of the cracked gas stream (full-range butadiene concentrate). In this case, the carbon number distribution is between C3 and C12 or even higher. Normally the C4+ full-range butadiene concentrate is split by distillation into two streams, a butadiene concentrate stream, described above, and pyrolysis gasoline stream. The C3+ stream is separated into these two streams plus a C3 stream. The C3 stream and pyrolysis gasoline will be covered by separate test categories sponsored by the CMA Olefins Panel. There are only two known examples where these broad-range streams have been reported to have been isolated. In both cases, it was a result of a shutdown of process equipment. The C4+ stream was site limited and the C3+ was not. The 1,3-butadiene content of full range butadiene concentrate has been reported to range from 12% to 42% (table 2).

4. 1,3-Butadiene

High purity 1,3-butadiene (99.5%+) is produced by separation from the C4 butadiene concentrate (or crude butadiene) produced by the ethylene process. This separation is accomplished by using a solvent process, either extraction or more typically extractive distillation. “On purpose” units also produce a small percentage of the commercially available 1,3 butadiene by dehydrogenation and subsequent separation.

Figure 1. Flowsheet for Crude Butadiene C4 Test Group

Note: In addition to Crude Butadiene C4 products & streams, additional HPV products & streams associated with these units are show below for clarity.

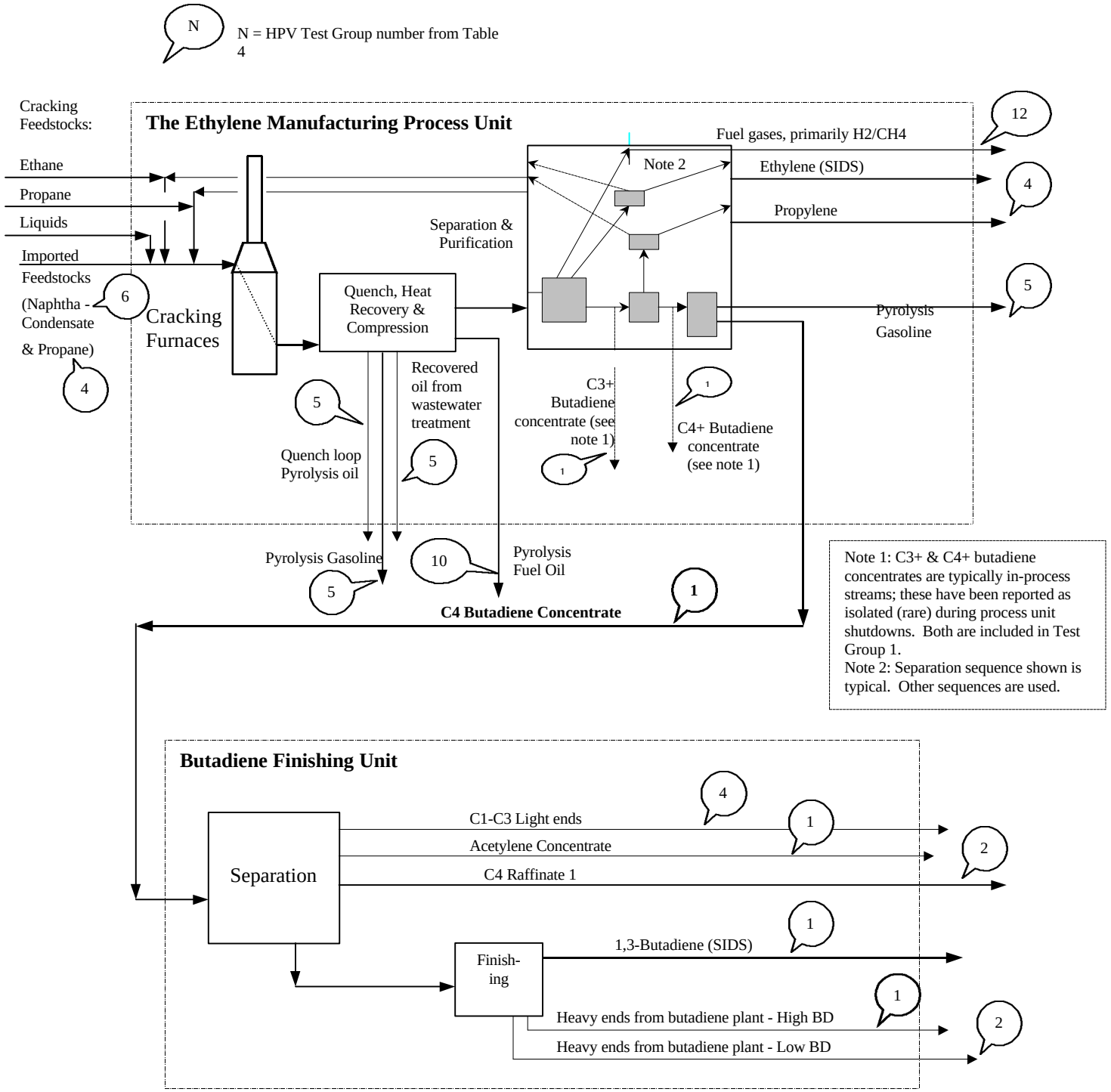

Table 4. CMA Olefins Panel Sponsored Test Categories

Category Number	Category Description
1	Crude Butadiene C4
2	Low Butadiene C4
3	C5 Non-Cyclics
4	Propylene Streams (C3)
5	High Benzene Naphthas (C6-C12, predominantly C6)
6	Low Benzene Naphthas (C7-C12)
7	Resin Oil - High Dicyclopentadiene
8	Resin Oil - Low Dicyclopentadiene
9	Resin Oil - Dicyclopentadiene Concentrate and Crude Dicyclopentadiene
10	Fuel Oils (C8+)
12	Fuel Gases

Robust Summary - Group 1: High Butadiene C4

Acute Toxicity

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	OECD 402.
Type (test type)	Acute inhalation.
GLP	Yes.
Year	1982.
Species/Strain	Rat/Fischer 344.
Sex	Males and females.
No. of animals per sex per dose	5/sex.
Vehicle	Not applicable.
Route of administration	Inhalation (gas).
Test Conditions	A group of ten rats (age: 12 weeks, weight: 143-234 grams) were exposed to 5300 mg/m3 (2331 ppm) of the test substance in air for four hours. Analytical chamber concentrations were determined by gas chromatography every 15 minutes during the exposure; a single particle size sample was taken to show the absence of aerosol. Body weights were recorded prior to exposure and 7 and 14 days post-exposure. Individual clinical observations were recorded pre-exposure and daily for 14 days post-exposure. The rats were sacrificed on the fourteenth day and a gross necropsy performed.
Results	
LC50	Rat LC50 (4 hour) = >5300 mg/m3 (2331 ppm).
Remarks	Observations noted following exposure were two male rats with respiratory sounds/wheezing or hyperexcitability and one female with minimal porphyrin around the eyes. All rats were normal from Days 2-14. No significant necropsy findings were reported, except one female with an ovary filled with red fluid. Body weight gains appeared normal.
Conclusions	
(study author)	No mortality or significant adverse effects were observed in rats exposed to 5300 mg/m3 (2331 ppm) of the test substance.
Data Quality	
Reliability	Reliable without restrictions. Guideline study.
References	Gulf Oil Chemicals Company (1982). Acute LC50 Inhalation Toxicity Test in Rats with Butadiene Feedstock. Unpublished report (Project #82-060).
Other	Robust Summary prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	19-Oct-99

Robust Summary - Group 1: High Butadiene C4

Acute Toxicity

Test Substance	1,3-butadiene CAS# 106-99-0
Method	
Method/guideline followed	Other.
Type (test type)	Acute inhalation.
GLP	Pre-GLP.
Year	1969.
Species/Strain	Rat and mouse (strains not specified).
Sex	Not specified.
No. of animals per sex per dose	Not specified.
Vehicle	Not applicable.
Route of administration	Inhalation (gas).
Test Conditions	Age, number, and sex of test animals not specified. Number of groups and exposure concentrations not specified. Dynamic flow exposure system; no description of exposure chambers or conditions. Rats exposed four hours; mice exposed two hours. No post-exposure observation period - mortality study only. Exposure concentrations "controlled" by gas chromatography.
Results	
LC50 with confidence limits	Rat LC50 (4 hour) = 285 mg/L (219-370 mg/L $p \leq 0.05$) Mouse LC50 (2 hour) = 270 mg/L (251-290 mg/L $p \leq 0.05$)
Remarks	No clinical observations or necropsy findings reported. Objective of study was to determine hydrocarbon concentrations in various tissues at lethal exposure concentrations.
Conclusions	
(study author)	LC50 value reported to be 285 mg/L (129,000 ppm) in rats, 270 mg/L (122,000 ppm) in mice.
Data Quality	
Reliability	Not assignable. Lethality study only; insufficient experimental detail to assess quality.
References	Shugaev, B.B. (1969) Concentrations of Hydrocarbons in Tissues as a Measure of Toxicity. Arch. Environ. Health 18:878-882.
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	13-Oct-99

Robust Summary - Group 1: High Butadiene C4

Acute Toxicity

Test Substance	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene
Method	
Method/guideline followed	Other.
Type (test type)	Irritation screen in rabbits.
GLP	Yes.
Year	1985.
Species/Strain	Rabbit (New Zealand White).
Sex	1 male, 1 female.
Vehicle	Not applicable.
Route of administration	Eye and skin.
Remarks For Test Conditions	Two young adult rabbits were evaluated for eye and skin irritation. The test substance was dispensed immediately prior to dosing into a flask packed in dry ice. On the first treatment day, 0.1mL of the test substance was instilled into one eye of each rabbit. Irritation was scored at 24, 48, and 72 hours. The untreated eye served as the control. Twenty-four hours after treatment of the eye, 0.1mL of the test substance was applied to the skin of the rabbits and occluded with a rubber dam. The test sites were evaluated 1, 3, and 7 days after dosing.
Results	
Remarks	The eye irritation scores were 0 at all observation intervals. The treated skin sites were virtually free of irritation at all observation intervals.
Conclusions	
(study author)	The test substance is estimated not to be irritating to the eye or skin.
Data Quality	
Reliability	Reliable with restrictions. Screening study.
References	Mobil Environmental and Health Sciences Laboratory (1985). Irritation Screen of Butadiene Concentrate in Albino Rabbits, Unpublished report (Study No. 41652).
Other	Robust Summary prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	24-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Test substance	1,3-butadiene CAS# 106-99-0
Method	
Method/guideline followed	No data.
Type	Reverse mutation assay (Ames *Salmonella* test).
System of testing	Bacterial.
GLP	No data.
Year	1990.
Species/Strain	Salmonella typhimurium/TA97, TA98, TA100, TA1535.
Metabolic activation	With and without.
Species and cell type	Rat, mouse, and human liver S9 fraction.
Quantity	0.8 and 4.0 mg protein/plate.
Induced or not induced	Arochlor 1254-induced and uninduced rat, mouse, and human S9.
Concentrations tested	0, 30, 40, 50, and 60% butadiene in air.
Statistical Methods	Not specified.
Remarks for Test Conditions	Concentrations of butadiene gas were metered into specially constructed treatment chambers holding the agar plates overlaid with the bacteria and activation system. Actual gas concentrations were determined by gas chromatography before and after the 48 hour exposure period. Different treatment chambers were used for each activation system and for the non-activated treatment. S9 preparations were made according to the procedure of Ames et al. (1975).
Results	1,3-Butadiene (BD) induced revertants only in strain TA1535. Mouse S9 showed slightly higher activity than the uninduced rat or human S9 at 30% BD in air. At concentrations greater than 30%, the number of revertants decreased in the presence of rat or human S9. Results from the human S9-activated treatments did not differ substantially from those of the non-activated treatments. Arochlor 1254-induced rat S9 gave similar results as mouse S9 (uninduced). Since the response was weak, the S9 concentration was increased from 0.8 mg/plate to 4.0 mg/plate. Increasing the concentration of Arochlor 1254-induced rat S9 had no effect on the number of revertants; slightly more revertants were observed using 4.0 than 0.8 mg/plate of uninduced rat S9.
Conclusions	
(study author)	*Salmonella typhimurium* reverse gene mutation (Ames) tests of 1,3-butadiene using strains TA1535, TA97, TA98, and TA100 and employing rat, mouse, and human liver S9 metabolic systems were barely 2-fold above background only in strain TA1535 at 30% butadiene in air with induced and uninduced rat S9 and mouse S9 (uninduced). In general, 1,3- butadiene was a weak *in vitro* genotoxin.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.
Reference	Arce G.T., Vincent D.R., Cunningham M..J, Choy W.N., and Sarrif A.M. (1990). In vitro and in vivo genotoxicity of 1,3-butadiene and metabolites. Environ. Health Perspect. 86:75-8.
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Test substance	Butadiene Concentrate, CAS# 68955-28-2. Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	OECD 482.
Type	Unscheduled DNA Synthesis (UDS).
System of testing	Primary hepatocytes derived from Fischer 344 rats.
GLP	Yes.
Year	1984.
Metabolic activation	No.
Concentrations tested	0, 1000, 5000, 10000, and 20000 ppm.
Control groups and treatment	Negative = air only; positive = 2-acetylaminofluorene (0.2ug/mL).
Statistical Methods	Group means and standard deviations for number of viable cells and nuclear grain counts. The test substance was considered positive if the mean nuclear grain count exceeded the negative control by at least 6 grains per nucleus and the negative control did not exceed 5.
Remarks for Test Conditions	Primary hepatocytes were derived from freshly perfused rat liver (1 male, 10 weeks age, 226 grams body weight). Cultures were seeded with approximately 10^5 cells/mL on Day 1. Three cultures per group were exposed to ^{3}H-thymidine and the test substance for 18-20 hours. The culture flasks were placed in sealed dessicator jars for the exposure period, and the test substance added by injection via a 50cc syringe. Cells growing on coverslips were fixed on Day 2. On Day 3 the slides were dipped in autoradiograph emulsion and stored in the dark at 2-8^{o}C. The autoradiographs were developed and stained on Day 21.
Results	A separate range-finding study was conducted to establish levels of cytotoxicity based on relative cell viability. The test substance was toxic to primary hepatocytes at 10000 ppm where 64% relative viability was observed following 18 hour exposure. At 20000 ppm, the relative viability was 57%. In the UDS study, both positive and negative control groups gave expected responses. A weak positive response was observed at 20000 ppm (7.74 nuclear grain counts vs. 1.24 in the air control vs. 107.13 in the positive control). The 1000, 5000, and 10000 ppm groups were also slightly increased (4.29-5.14) from the air control but less than the criteria for a significant response.
Conclusions	
(study author)	Cytotoxicity was observed at 10000 ppm. Increased unscheduled DNA synthesis was observed at 20000 ppm.
Data Quality	
Reliabilities	Reliable without restrictions. Guideline study.
Reference	Gulf Oil Chemicals Company (1984). Hepatocyte Primary Culture/DNA Repair Test of Butadiene Feedstock, Unpublished report (Project# 2073).
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
L*ast changed*	18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Test substance	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	Other.
Type	Mammalian cell transformation test.
System of testing	BALB/3T3-A31-1-1 cells.
GLP	Yes.
Year	1983.
Metabolic activation	No.
Concentrations tested	0, 1000, 5000, 10000, and 20000 ppm.
Control groups and treatment	Negative = air only; positive = 3-methylcholanthrene (1.0 ug/mL).
Statistical Methods	Group means and standard deviations for number of viable cells, cloning efficiency, and transformed foci per culture. The test substance was considered positive if there was a two-fold increase in foci compared to the negative control group.
Remarks for Test Conditions	Each treatment group consisted of 12 flask cultures for cell transformation seeded with 10000 cells and 2 plate cultures for cloning efficiency with 250 cells. The cultures were placed in sealed dessicator jars and exposed to the test substance for two days. The test substance was added to the jars by injection via a 50cc syringe and samples of the exposure atmosphere were analyzed by gas chromatography. The mediums were changed on Day 4 and then weekly. Plate cultures were fixed and stained on Day 8 and flask cultures on Day 29. Foci in transformation cultures were counted and examined microscopically to determine type.
Results	Cloning efficiency was used as a measure of toxicity under culture conditions. Toxicity was observed at 5000 ppm where a relative cloning efficiency of 53.8% was observed. The negative and positive control gave expected responses for transformation. The response for the test substance was not increased from the negative control group at any level tested.
Conclusions	
(study author)	The test substance was negative for cell transformation.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to draft OECD guideline.
Reference	Gulf Oil Chemicals Company (1983). BALB/3T3 Transformation Test Using Butadiene Feedstock, Unpublished report (Project# 2074).
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene.
Method	
Method/guideline followed	No data.
Type	Reverse mutation assay (Ames *Salmonella* test).
System of testing	Bacterial.
GLP	Yes.
Year	1985.
Species/Strain	Salmonella typhimurium/ TA98, TA100, TA1535, TA1537, TA1538.
Metabolic activation	With and without.
Species and cell type	Rat liver S9 fraction.
Quantity	0.6 mL.
Induced or not induced	Arochlor 1254-induced.
Concentrations tested	25, 50, 75, or 100 uL.
Statistical Methods	The test substance was considered mutagenic if it produced a dose-related two-fold increase in mean revertant value compared to the negative control.
Remarks for Test Conditions	The test substance was stored in a dry ice/ethanol slurry to prevent loss of volatile components and dosed by microdispenser into sterile septa-capped culture tubes. Sodium phophate buffer or S-9/bacteria mix was injected through the septa into the tubes containing the test substance and pre-incubated for 20 minutes at 37^{o}C. After the pre-incubation period, the contents of the tubes were overlayed on agar and incubated for 48 hours at 37^{o}C. Revertant colonies were counted by automatic colony counter. Positive control chemicals were: 2.0 ug 2-aminoanthracene, 15.0 ug 9-aminoacridine, 20.0 ug 2-nitrofluorene, and 5.0 ug N-methyl-N-nitro-N-nitrosoguanidine, in 50 uL DMSO per plate.
Results	A preliminary toxicity/initial mutagenicity assay was conducted over a range of 10 to 500 uL per plate in two strains (TA100 and TA1537) with and without S-9. Toxicity was exhibited at $\geq$75uL in TA100, and $\geq$100uL in TA1537. Some inconsistencies in toxicity with increasing dose level were noted that were attributed to the volatility of the test substance. Based on the toxicity data, the test substance was tested in the pre-incubation mutagenicity assay at volumes of 25, 50, 75, and 100 uL per plate. None of the five strains with or without induced rat liver S-9 exhibited reversion frequencies substantially different from spontaneous controls in this assay.
Conclusions	
(study author)	The test substance was not considered a mutagen with or without metabolic activation in this test system.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.
Reference	Mobil Environmental and Health Sciences Laboratory (1985). An Ames Salmonella/Mammalian Microsome Mutagenesis Assay For Determination of Potential Mutagenicity of Butadiene Concentrate, Unpublished report (Study No. 41653).

Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	24-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene.
Method	
Method/guideline followed	Other.
Type	Mouse lymphoma mutagenesis assay.
System of testing	Mammalian cell.
GLP	Yes.
Year	1985.
Species/Strain	Mouse lymphoma cells/ L5178Y (TK+/-; subclone 3.7.2C).
Metabolic activation	With and without.
Species and cell type	Rat liver S9 fraction.
Quantity	4.0 mL.
Induced or not induced	Arochlor 1242/1254-induced.
Concentrations tested	Nonactivated assays: 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 35.0 40.0, or 45.0 uL/mL media. S-9 activated assays: 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, or 25.0 uL/mL.
Statistical Methods	The test substance was considered mutagenic if it produced a dose-related or toxicity-related two-fold increase in average mutant frequency compared to the negative controls, at concentrations exhibiting acceptable total growths (10% or greater).
Remarks for Test Conditions	The positive control chemical for the S-9 activated assays was 7, 12-dimethylbenz[a]anthracene (DMBA) at 2.5 and 5.0 ug/mL, and ethylmethane sulfonate (EMS) for the nonactivated assays at 0.5 and 1.0 uL/mL. An initial toxicity assay was performed with and without activation at concentrations ranging from 10 to 100 uL/mL. The dosing regimen for the mutagenesis assay was designed to produce 10-90% lethality. Six mLs of cell suspension (10^6 cells/mL) were exposed for 3 hours to the test or positive control substances. An expression period of 2 days followed with determinations of cell population densities and growth. Cultures selected for mutant analysis and cloning efficiencies were incubated for 10-12 days.
Results	Without activation, mutant frequencies and total number of mutants were significantly increased at the two highest concentrations (20.0 and 22.5 uL/mL). Although total growth was very low (5.1% and 5.5%), these levels were considered mutagenic since there was no reduction in cloning efficiency. There were no significant differences in mutant frequency for the S-9 activated cultures.
Conclusions	
(study author)	The test substance induced a significant increase in mutant frequency of mouse lymphoma cells without metabolic activation, but was evaluated as non-mutagenic in the presence of S-9 activation.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.

Reference	Mobil Environmental and Health Sciences Laboratory (1985). Evaluation of the Mutagenic Potential of Butadiene Concentrate in the Mouse Lyphoma (L5178Y/TK+/-) Mutagenesis Assay, Unpublished report (Study No. 41654).
Other *Last changed*	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 24-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vivo

Test Substance	
Remarks	1,3-butadiene CAS# 106-99-0
Method	
Method/guideline followed	Other.
Type	Mammalian erythrocyte micronucleus assay.
GLP	No data.
Year	1994.
Species	Rat and mouse.
Strain	Rat: Wistar. Mouse: CB6F1
Sex	Rat: Male. Mouse: Female.
Route of administration	Inhalation (gas).
Doses/concentration levels	0, 50, 200, or 500 ppm.
Exposure period	6 hours/day for 5 days.
Statistical methods	Student's two-tailed t-test for differences between groups.
Remarks for Test Conditions.	Twenty female CB6F1 mice (approximately 25g, 8-10 weeks old) and ten male Wistar rats (300-350g, 10 weeks old) per group were exposed for 5 days, 6 h/day 0, 50, 200, or 500 ppm of 1,3-butadiene (BD) by inhalation. An additional high concentration group of mice was exposed to 1300 ppm. Exposure concentrations were monitored by infrared spectroscopy (rats) and gas chromatography (mice). The animals were sacrificed 1 day after the last exposure and smears of blood and bone marrow erythrocytes were prepared and stained.
Results	In the rats, no effects on micronuclei frequencies were observed either in the peripheral blood or bone marrow at all exposure levels. A slight toxic effect in rat bone marrow cells (decreased polychromatic/normochromatic ratio) was observed at the 500 ppm level. In the mice, a clear dose-dependent increase in micronuclei frequency was observed in both blood and bone marrow cells at all exposure levels tested.
Conclusions	
(study author)	1,3-butadiene was active in inducing micronuclei in peripheral blood and bone marrow erythrocytes in mice at levels $\geq$50 ppm, but not in rats. The genotoxic effects observed in this study parallel the species differences observed in cancer studies.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.
References	Autio, K., Renzi, L., Catalan, J., Albrecht, O.E., and Sorsa, M. (1994). Induction of Micronuclei in Peripheral Blood and Bone Marrow Erythrocytes of Rats and Mice Exposed to 1,3-Butadiene by Inhalation. Mut. Res. 309:315-320.
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	25-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in vivo

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	OECD 474.
Type	Mammalian erythrocyte micronucleus test.
GLP	Yes.
Year	1984.
Species	Mouse.
Strain	Crl:CD-1 BR Swiss.
Sex	Male and female.
Route of administration	Inhalation (gas).
Doses/concentration levels	10780, 20671, 35430 ppm.
Exposure period	2 hours/day for 2 consecutive days.
No. of animals per dose	10/sex/group.
Control groups and treatment	10/sex negative (air) control; 5/sex positive control (cyclophosphamide, 75 mg/kg intraperitoneal injection).
Statistical methods	Group mean body weights, total polychromatic erythrocytes (PCEs), normochromatic erythrocytes (NORMs), PCEs with micronuclei, and NORMs with micronuclei were compared by t-test ($p<0.05$ = positive).
Remarks for Test Conditions.	Mice were 11 weeks old and 25-42 grams weight at study initiation. Test and control substances were administered on Days 1 and 2. Exposure concentrations determined by gas chromatography. Animals were observed daily and body weights were recorded on Days 1, 3, and 4. Five mice/sex/group were sacrificed on Days 3 and 4 and bone marrow smears prepared; positive controls (5/sex) were sacrificed on Day 3 only.
Results	No mice died during the study; the only clinical observations were an apparent unconsciousness during exposure. There were no significant body weight differences. The negative and positive control groups produced negative and positive resulats, respectively. Mice in the exposed groups showed increased micronuclei formation at all levels in both sexes. Females were statistically increased from control at all levels on Day 3 and at 20671 ppm and 35430 ppm on Day 4; males were significantly increased only at 35430 ppm on both days. There was no significant change in the PCE/NORM ratio in any group.
Conclusions	
(study author)	The test material produced an increased frequency of micronucleated erythrocytes in the bone marrow of mice at all levels tested.
Data Quality	
Reliabilities	Reliable without restrictions. Guideline study.
References	Gulf Oil Chemicals Company (1984). Micronucleus Test in Mouse Bone Marrow: Butadiene Feedstock Administered by Inhalation For 2 Hours/Day For 2 Days, Unpublished report (Project #2014).
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	13-Oct-99

Robust Summary - Group 1: High Butadiene C4

Repeated Dose Toxicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Rubber grade, containing 0.02% t-butyl catechol; purity ≥98.94%.
Method	
Method/guideline followed	Other.
Test type	14-week inhalation study.
GLP	Yes.
Year	1977.
Species	Mouse.
Strain	B6C3F1.
Route of administration	Inhalation (gas).
Duration of test	14 weeks.
Doses/concentration levels	0, 625, 1250, 2500, 5000, or 8000 ppm.
Sex	10 male, 10 female per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days/week, total of 63 or 64 exposures.
Control group and treatment	10 male, 10 female, air-only exposed.
Post exposure observation period	Not applicable.
Statistical methods	Group means and standard deviations calculated for body weights.
Test Conditions	Groups of 10 mice/sex /group (4-5 weeks age at study initiation) were exposed to various levels of 1,3-butadiene for 6 hrs/day, 5 days/week for 14 weeks (64 exposures). Because four male mice in the high exposure group died by day 4, another 2 groups of 10 male mice each were restarted (control and 8000 ppm). Mice were observed once daily for morbidity and mortality; moribund animals were sacrificed. Body weights were recorded weekly. At the end of the 95 or 93-day (restart) studies, surviving mice were sacrificed. Necropsies were performed and tissues preserved. Histopathologic examinations were performed on all controls, high exposure (8000 ppm), and early deaths.
Results	
NOAEL (NOEL)	1250 ppm.
LOAEL (LOEL)	2500 ppm, based on reduced body weight gains.
Remarks	Six of ten males and 1/10 females exposed at 8000 ppm, 6/10 males and 1/10 females at 5000 ppm, and 1/10 males at 2500 or 1250 ppm died prior to study termination or were sacrificed in a moribund condition. Body weight gains were decreased in males at 2500, 5000, and 8000 ppm, and at 5000 and 8000 ppm in the females. No exposure-related histopathologic effects were observed in the high (8000 ppm) group.
Conclusions	Based on the results of this study, exposure levels of 625 and 1250 ppm were selected for a 2-year carcinogenicity study in mice based on reduced body weight gains and mortality in higher exposure groups.
Data Quality	
Reliabilities	Reliable with restrictions. Acceptable, well-documented study report but deficient by current guidelines. No organ weights, hematology or clinical chemistry evaluations were performed.

References	National Toxicology Program, Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies), NTP Technical Report Series No. 288, NIH Publication 84-2544 (1984).
Other Last changed	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 8-Dec-99

Robust Summary - Group 1: High Butadiene C4

Repeated Dose Toxicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity >99.2%, containing 120 ppm t-butyl catechol.
Method	
Method/guideline followed	Other.
Test type	13-week inhalation study.
GLP	No data.
Year	1977.
Species	Rat.
Strain	CD (Sprague-Dawley).
Route of administration	Inhalation (gas).
Duration of test	14 weeks.
Doses/concentration levels	0, 1000, 2000, 4000, or 8000 ppm.
Sex	40 male, 40 female per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days/week for 13 weeks.
Control group and treatment	40 male, 40 female, exposed to filtered air only.
Post exposure observation period	Not applicable.
Statistical methods	Analysis of variance for body weights, food consumption, urinalysis, hematology, clinical chemistry, organ weights.
Test Conditions	Groups of 40 rats/sex /group (approx. 5 weeks age at study initiation) were exposed to various levels of 1,3-butadiene for 6 hrs/day, 5 days/week for 13 weeks. All animals were observed daily; individual body weights and food consumption were recorded weekly. Interim sacrifices of 10 rats/sex/group were performed after 2 and 6 weeks of exposure. Three urine samples were obtained from each animal during the 1-2 weeks prior to sacrifice. Blood samples were collected from all rats prior to the 2, 6, and 13 week sacrifices. Brain cholinesterase activity was measured using half the brain of 5 rats/sex/group at the 2 and 6-week sacrifices and all rats at the terminal sacrifice. Organ weights were recorded for the adrenals, brain, gonads, heart, kidneys, liver, lung, pituitary, spleen, and thyroid. Necropsies were performed and tissues preserved. Histopathologic examinations were performed on all control and high exposure (8000 ppm) tissues.
Results	
NOAEL (NOEL)	8000 ppm.
LOAEL (LOEL)	>8000 ppm.
Remarks	Increased salivation was observed in the females after 8 weeks exposure and decreased grooming (stained fur) in the males after 10 weeks. No other exposure-related conditions were observed. Male rats showed slight (non-statistically significant) reductions in body weight gains compared to the controls; female body weights at 1000 and 4000 ppm were statistically higher than the controls. Neuromuscular function tests using a modified rotating cone gave some random group differences, but were not considered exposure-related. There were no toxicologically significant differences in hematology, blood chemistry, brain cholinesterase measurements, or urine analysis. Organ weight and organ to brain weight ratios showed some scattered statistically significant differences among the groups but did not indicate any treatment-related effects.

	Microscopic examination of the tissues of the exposed rats showed a similar incidence and severity of histopathologic findings to the control group.
Conclusions (study author)	Rats exposed to butadiene gas at concentrations up to 8000 ppm showed no significant effects related to exposure.
Data Quality Reliabilities	Reliable without restrictions. Comparable to guideline study.
References	Crouch, C.N., Pullinger, D.H., and Gaunt, I.F. (1979) Inhalation Toxicity Studies With 1,3-butadiene - 2. 3 Month Toxicity Study in Rats. Am. Ind. Hyg. Assoc. J. 40:796-802.
Other Last changed	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Developmental Toxicity/Teratogenicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	OECD 414.
Test type	Developmental toxicity (teratogenicity) study.
GLP	Yes.
Year	1987.
Species	Mouse.
Strain	CD-1 (Swiss).
Route of administration	Inhalation (gas).
Concentration levels	0, 40, 200, or 1000 ppm.
Sex	18-22 pregnant females per group.
Exposure period	Days 6-15 of gestation.
Frequency of treatment	6 hours/day.
Control group and treatment	Air-exposed only.
Duration of test	Females sacrificed on gestation day 18.
Statistical methods	Analysis of variance for body weights, number of resorptions, implants, live, dead or affected fetuses per litter. Significant differences among the groups were also analyzed by Duncan's multiple range test or arcsin transformation of the response proportion. Binary-response variables were between groups were compared using chi-square or Fisher's exact test.
Remarks for Test Conditions.	Female mice were mated to unexposed males and exposed from days 6-15 of gestation to 0, 40, 200, or 1000 ppm of the test substance. Analytical chamber concentrations were measured by on-line gas chromatography. Body weights were recorded on gestation days 0, 6, 11, 16, and 18. Maternal animals were observed daily for mortality, morbidity, and signs of toxicity and examined for gross tissue abnormalities at necropsy (day 18). The uterus and placenta was removed and weighed; the number of implantation sites, resorptions, live and dead fetuses were recorded. Live fetuses were weighed and subjected to external, visceral, and skeletal examinations. Approximately 50% of the fetal heads were sectioned and examined.
Results	
NOAEL maternal toxicity	40 ppm.
NOAEL developmental toxicity	40 ppm. There were decreases in maternal body weight gains in the 200 and 1000 ppm groups. Fetal weights were significantly reduced in both males and females at 200 and 1000 ppm; placenta weights were significantly reduced for corresponding male fetuses at 200 ppm and for both males and females at 1000 ppm. There were no significant differences in percent resorptions or malformations per litter, although there was an increase in fetal variations (supernumary ribs and reduced ossification of sternebrae) at 200 and 1000 ppm.
Conclusions	
(study author)	Developmental toxicity was observed in mice in the presence of maternal toxicity at 200 and 1000 ppm. A slight statistically significant decrease in male fetal weight (95% of control) was also observed, but the biological significance of this finding has been questioned.

Data Quality *Reliabilities*	Reliable without restrictions. Guideline study.
References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other Las*t changed*	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 20-Oct-99

Robust Summary - Group 1: High Butadiene C4

Developmental Toxicity/Teratogenicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	OECD 414.
Test type	Developmental toxicity (teratogenicity) study.
GLP	Yes.
Year	1987.
Species	Rat.
Strain	CD (Sprague-Dawley).
Route of administration	Inhalation (gas).
Concentration levels	0, 40, 200, or 1000 ppm.
Sex	24-28 pregnant females per group.
Exposure period	Days 6-15 of gestation.
Frequency of treatment	6 hours/day.
Control group and treatment	Air-exposed only.
Duration of test	Females sacrificed on gestation day 20.
Statistical methods	Analysis of variance for body weights, number of resorptions, implants, live, dead or affected fetuses per litter. Significant differences among the groups were also analyzed by Duncan's multiple range test or arcsin transformation of the response proportion. Binary-response variables between groups were compared using chi-square or Fisher's exact test.
Remarks for Test Conditions.	Female rats were mated to unexposed males and exposed from days 6-15 of gestation to 0, 40, 200, or 1000 ppm of the test substance. Analytical chamber concentrations were measured by on-line gas chromatography. Body weights were recorded on gestation days 0, 6, 11, 16, and 20. Maternal animals were observed daily for mortality, morbidity, and signs of toxicity and examined for gross tissue abnormalities at necropsy (day 20). The uterus and placenta was removed and weighed; the number of implantation sites, resorptions, live and dead fetuses were recorded. Live fetuses were weighed and subjected to external, visceral, and skeletal examinations. Approximately 50% of the fetal heads were sectioned and examined.
Results	
NOAEL maternal toxicity	200 ppm
NOAEL developmental	1000 ppm
toxicity	The only toxicity observed was decreased body weight gains in the dams at 1000 ppm. The percentage of pregnant animals and number of litters with live fetuses were unaffected by treatment. There were no significant differences among the groups for number of live fetuses per litter, percent resorptions or malformations per litter, placental or fetal body weights, or sex ratio.
Conclusions	
(study author)	There was no evidence of teratagenicity or adverse reproductive effects in any of the exposed groups.
Data Quality	
Reliabilities	Reliable without restrictions. Guideline study.

References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other La*st changed*	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 20-Oct-99

Robust Summary - Group 1: High Butadiene C4

Toxicity to Reproduction

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	Other.
Test type	Sperm-head morphology assay.
GLP	Yes.
Year	1987.
Species	Mouse.
Strain	B6C3F1.
Route of administration	Inhalation (gas).
Concentration levels	0, 200, 1000, and 5000 ppm.
Sex	20 males per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days.
Control group and treatment	Air-exposed only.
Duration of test	Males sacrificed 5 weeks post-exposure.
Statistical methods	Normal and abnormal sperm heads were expressed as percentage of the total number of cells examined. These data were subjected to arcsin transformation and evaluated by analysis of variance. If significant, Duncan's multiple range test was used for intergroup differences. Dose response trends were determined by orthogonal contrast.
Remarks for Test Conditions.	The mice were observed twice daily and body weights recorded weekly. During the fifth week post-exposure the mice were sacrificed and examined for lesions of the reproductive tract and other gross abnormalities. Sperm was obtained from the cauda of the right epididymis. Slides were prepared, stained, and examined microscopically. The morphology of at least 500 sperm heads per mouse was categorized.
Results	
NOAEL	200 ppm
	The percentage of abnormal sperm heads increased with exposure concentration: 1.61% (0 ppm), 1.95% (200 ppm), 2.79% (1000 ppm), and 3.79% (5000 ppm). Only the values for the 1000 and 5000 ppm groups were significantly different from the control ($p < 0.05$). Only a single timepoint was examined, so the effect on all stages of spermatogenesis could not be determined.
Conclusions	
(Study author)	These results suggest that the test substance affected spermatogenesis in mice at 1000 and 5000 ppm, but the effect of this observation on other reproductive endpoints is not known.
Data Quality	
Reliabilities	Reliable with restrictions. Acceptable, well-documented publication which meets basic scientific principles.

References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other La*st changed*	Robust Summaries Prepared by ExxonMobil Biomedical Sciences, Inc. 20-Oct-99

.**Robust Summary - Group 1: High Butadiene C4**

Toxicity to Reproduction

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	Other.
Test type	Rodent dominant lethal test.
GLP	Yes.
Year	1987.
Species	Mouse
Strain	CD-1 (Swiss).
Route of administration	Inhalation (gas).
Concentration levels	0, 200, 1000, and 5000 ppm.
Sex	20 males per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days.
Control group and treatment	Air-exposed only.
Duration of test	8 weeks post-exposure.
Statistical methods	The number of implantation sites and intrauterine deaths per litter for each week were analyzed by analysis of variance. When appropriate, proportions of resorptions and dead or live fetuses per implant were subjected to arcsin transformation and evaluated by analysis of variance. If significant, Duncan's multiple range test was used for intergroup differences.
Remarks for Test Conditions.	After five days of exposure, the male mice were mated with unexposed females (two females per week for each male for 8 consecutive weeks). Females were removed from cohabitation after 7 days sacrificed 12 days later and the uterine contents examined. Observations included: the total number, position, and status of implantations; the numbers of early and late resorptions; and numbers of live and dead fetuses.
Results	Slight statistically significant effects were noted in the mated females for three endpoints during the first 2 weeks post-exposure: ratio of dead to total implants, percentage of females with $\geq$2 dead implants, and number of dead implants per pregnancy. However, these observations only occurred in the two lower exposure groups (except for increased number dead implants/pregnancy in the 5000 ppm group during week 1). There were no differences for number of pregnant females, implantations per litter, number of live fetuses, dead implantations per total implantations, or number of resorptions during weeks 1 and 2. There were no differences for any endpoint during weeks 3-8.
Conclusions	
(Study author)	The authors concluded that the results observed during the first two weeks are consistent with an adverse effect on more mature germ cells (spermatozoa and spermatids) however considering the lack of effects in the high exposure group the findings are not clear for a dose-dependent response.
Data Quality	
Reliabilities	Reliable with restrictions. Acceptable, well-documented publication which meets basic scientific principles.

References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other La*st changed*	Robust Summary Prepared by Exxon Biomedical Sciences, Inc. 20-Oct-99